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IAP86
OCT 17 2006
PATENT & TRADEMARK OFFICE

Application No.:	10/729,830
Applicant:	Von Der Mulbe, *et al.*
Filed:	December 5, 2003
Title:	PHARMACEUTICAL COMPOSITION CONTAINING A STABILISED MRNA OPTIMISED FOR TRANSLATION IN ITS CODING REGIONS
Art Unit:	1636
Confirmation No.:	8653
Examiner:	Dunston, Jennifer Ann
Docket No.:	075067-0501 (CRVC-001 US)

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION OF DR. INGMAR HOERR UNDER 37 C.F.R. § 1.132

Dear Sir:

I, Ingmar Hoerr, hereby declare that:

1. I am one of the inventors of the invention disclosed in the above-identified patent application ("the '830 application"), and, thus, I am familiar with the application and the invention claimed therein.

2. I hold a doctorate from the University of Tuebingen, Germany. My doctorate research was on RNA vaccines. I have several years of experience and active scientific research activity, and numerous publications in the field of mRNA and, more specifically, stabilized mRNA. A *curriculum vitae* is attached herewith as **Exhibit A**.

3. I am a founder of and I presently hold the position of Chief Executive Officer of CureVac GmbH in Tuebingen, Germany, the Assignee of the '830 application.

4. I have reviewed and understand the Office Action mailed April 17, 2006. I am submitting this declaration to respond to some of the Examiner's comments regarding the .

5. The Examiner seems to be concerned that the patent application does not provide working examples showing therapeutic effects. For example, the April 17, 2006 Office Action states: "While the specification and working examples teach how to make a modified mRNA that meets the structural characteristics of the claimed invention, the specification does not teach how to use the pharmaceutical compositions for any therapy. No working examples that demonstrate a therapeutic outcome are provided." Office Action at pages 7-8. With respect to the state and predictability of the art, the Examiner stated that: "The use of RNA for vaccination is unpredictable in that the process depends upon cell-specific and tissue-specific efficient transfer of the nucleic acid... Furthermore, the success of nucleic acid vaccination is unpredictable with regard to obtaining a prophylactic or therapeutic effect..." Office Action at pages 8-9.

6. A series of studies are described in the attached **Exhibit B** that are believe to address the Examiner's concerns. The studies were conducted using compositions of the claimed invention (*i.e.,* compositions comprising at least one modified mRNA that encodes at least one biologically active or antigenic polypeptide and a pharmaceutically compatible carrier

and/or vehicle, wherein the modified mRNA comprises an increase in G/C content relative to that of a wild type mRNA, and comprises a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA, and said abundant and rare cellular tRNAs recognize the same amino acid; and wherein the modified mRNA and the wild type mRNA encode a polypeptide comprising an identical amino acid sequence). The modified mRNA sequences are provided in the attached **Exhibit C**.

***IN VIVO* IMMUNIZATION OF MICE WITH OVALBUMIN mRNA – TUMOR SIZE REDUCTION**

7. Moore *et al.* demonstrated in 1988 that immunization of mice with Ovalbumin peptide led to the generation of Ovalbumin-specific cytotoxic T-cells which are able to kill cells expressing Ovalbumin (*Cell* 1988 Sep 9;54(6):777-85).

8. This mouse animal model was used in Study 3 in **Exhibit B** to compare the preventive vaccination of mice with wild type mRNA and GC-enriched mRNA coding for the antigen Ovalbumin. In this study, 20 µg mRNA (10 µg per ear) complexed with protamine were injected intradermally into the mice followed one day later with s.c. injection (subcutaneously) of GM-CSF. The immunization was repeated 7 times within 3 weeks.

9. As shown in the figure on page 6 of **Exhibit B**, immunization of mice with GC-enriched mRNA coding for Ovalbumin led to the formation of Ovalbumin-specific IgG1-antibodies, which indicates a humoral immune response against the antigen Ovalbumin. This resulted in the rejection of the tumor cells and a significant reduction in tumor size, as illustrated in the figures on pages 3-5 of **Exhibit B**. Mice vaccinated with the wild type mRNA also showed tumor rejection, but to a much lower extend than the mice which were vaccinated with GC-enriched mRNA. Study 3 clearly demonstrates that vaccination with protamine-complexed GC-enriched mRNA coding for an antigen is able to protect mice against tumor cells which express the antigen.

10. Study 3 demonstrated that injecting wild type mRNA for vaccination has the problem of a low expression of the antigen. To bypass this problem, scientists have used DNA-based vaccines which code for the antigen or *ex vivo* transfection of dendritic cells (reviewed in *Curr Opin Mol Ther.* 2000 Apr; 2(2):176-81). But DNA vaccinations present potential risks such as integration into the host genome or induction of pathogenic anti-DNA antibodies (reviewed in: *Springer Semin Immunopathol.* 1997;19(2):245-56). The disadvantage of *ex vivo* transfection of dendritic cells is that one have to culture, mature and expand the cells under GMP conditions which is very expensive and difficult (reviewed in: Expert Opin Biol Ther. 2004 Aug;4(8):1285-94). In contrast to this RNA can be produced inexpensively under GMP conditions and, by enrichment of the GC content of the mRNA coding for the antigen, we have shown that use of RNA-based vaccines yield a sufficient expression of the antigen. This result bypass the disadvantages of DNA-based vaccines and *ex vivo* transfection of dendritic cells.

***IN VIVO* IMMUNIZATION OF MICE AND *IN VITRO* TRANSFECTION OF HUMAN PBMCS WITH LUCIFERASE mRNA – LUCIFERASE EXPRESSION**

11. Additional evidence that GC-enriched mRNA has a higher therapeutic potential is provided in Study 4. Expression of Luciferase was measured 24h after intradermal injection of either wild type or GC-enriched mRNA coding for Luciferase. As illustrated in section 4.2 at page 6 of **Exhibit B**, GC-enriched mRNA coding for Luciferase resulted in

higher expression levels of Luciferase *in vivo* than wild type mRNA following interdermal injection in mice. Expression of Luciferase was also measured in human Peripheral Blood Mononuclear Cells (hPBMCs) following transfection of wild type or GC enriched mRNA coding for Luciferase in Study 6. As illustrated in section 6.2 at page 9 of **Exhibit B**, GC-enriched mRNA coding for Luciferase resulted in higher expression levels of Luciferase in hPBMCs than wild type mRNA following transfection. These results indicate that GC-enrichment of therapeutic mRNA solves the problem that mRNA is not stable in solution and leads to a low expression in vivo following administration and supports the use of the invention not only for genetic vaccination but also for gene therapy. The use of GC-enriched therapeutic mRNA also avoids the risks of DNA vaccination.

***IN VIVO* IMMUNIZATION OF MICE WITH INFLUENZA A MATRIX PROTEIN M1 (FLU) MRNA – CTL RESPONSE**

12. An effective immune response requires the induction of a cellular immune response (activation of cytotoxic T-cells and macrophages) and a humoral immune response (production of antibodies). Study 3 established that vaccination with GC-enriched mRNA leads to a higher antibody production against the antigen compared to the wild type mRNA, resulting in greater rejection of tumor cells and significantly smaller tumor size.

13. It is known that the generation of cytotoxic T-lypmphocytes (CTL) specific against tumor cells are important for the immune response to fight against the tumor (reviewed in *Ther. Immunol.* 1995 Jun;2(3):173-81). In Study 5, the induction of a CTL immune response was assessed in mice by vaccination with wild type or GC-enriched mRNA coding for the Influenza A matrix protein M1 (Flu) and the detection of apoptosis of target cells. As illustrated in section 5.2 at page 8 of **Exhibit B**, GC-enriched mRNA induced a higher CTL response specific against Flu and lysis of target cells compared to the wild type mRNA. These results indicate that, with GC-enriched therapeutic mRNA, more cytotoxic T-cells specific for the antigen are present, and are able to fight against cells which express the antigen.

***IN VITRO* IMMUNOSTIMULATORY EFFECTS OF INFLUENZA A MRNA IN HUMAN PBMCS – RELEASE OF IL-6 AND TNFα**

14. The release of the cytokines Interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) indicates the induction of an immune response. In Study 7, the effects of a wild type or a GC-enriched mRNA coding for Influenza A were assessed in hPBMCs. As illustrated in section 7.2 at page 10 of **Exhibit B**, GC-enriched mRNA coding for Influenza A, when incubated with hPBMCs, induced greater release of both IL-6 and TNFα compared to the wild type mRNA. These results provide further indication that GC-enriched therapeutic mRNAs induce an immune response, thereby inducing the lysis of the cells expressing the antigen.

***IN VIVO* VACCINATION OF HUMAN TUMOR PATIENT WITH MRNA CODING FOR SEVERAL TUMOR ANTIGENS – TUMOR REGRESSION AND INDUCTION OF ANTIBODY PRODUCTION**

15. In Study 8, a human patient with a renal cell carcinoma (see CT scan of the renal tissues) was injected intradermally four times with 150 µg mRNA coding for tumor antigens and viral antigens, including GC-enriched mRNA coding for hepatitis B surface (HBS) antigen, and wild type mRNA coding for CEA, Mucin-1, Her-2/neu, Survivin, MAGE-1, and

Influenza A Matrix protein M1 (Flu). Viral antigens were used in this trial to increase the immune response against the tumor antigens, because viral antigens are very immunogenic and, since most people have had an infection with influenza, the immune system becomes stimulated very strongly. The HBS antigen was additionally used as markers for induction of an immune response because the detection of HBS antibodies is a standard procedure in the clinic. The titer of antibodies against HBS were analyzed using a standard method in the clinic.

16. As illustrated in section 8.1 at page 12 of **Exhibit B**, a regression of the tumor was visible in the computer tomography (CT) scan of the renal tissues. The results also indicated that vaccination with mRNA coding for tumor antigens and viral antigens can induce antigen-specific antibodies, as indicated by the increase of the titer against the viral HBS antigen detected in the patient. See, section 8.2 at page 13 of **Exhibit B**.

17. In Study 9, a human patient with melanoma (see CT of the liver metastasis) was injected intradermally 11 times with 80 µg mRNA coding for tumor antigens and viral antigens, including GC-enriched mRNA coding for HBS antigen, and wild type mRNA coding for Melan-A, Tyrosinase, Survivin, MAGE-A3, MAGE-A1, gp100, and Influenza A Matrix protein M1 (Flu) complexed with protamine (5:1).

18. As illustrated in section 9.1 at page 14 of **Exhibit B**, a regression of the metastasis in the liver is also visible in the computer tomography (CT) scan of the liver tissue of this second patient.

19. These two clinical trials indicate that vaccination of tumor patients with mRNA coding for tumor antigens and viral antigens can induce the production of antigen-specific antibodies and induces the immune system to reject the tumor cells.

20. I declare further that all statements made in this Declaration of my own knowledge are true, that all statements made on information and belief are believed to be true, and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent that may issue from the present application.

Respectfully submitted,

Dr. Ingmar Hoerr

Date: 16-10-06

OIPE IAP86 OCT 17 2006 PATENT & TRADEMARK OFFICE

Exhibit A

Curriculum Vitae Dr. rer nat. Ingmar Hoerr

Name:	Dr. rer. nat. Ingmar Hoerr
Address:	Charlottenstr. 16
	D-72076 Tuebingen
Tel:	+49 7071 255213
Date of birth:	03.06.1968
Marital status:	Single
Nationality:	German

Education:

1985-1988	Agrarwissenschaftliches Gymnasium Nuertingen Certificate: A-Level
10/1988-06/1990	Alternative civilian service
10/1990-03/1995	Study of biology at the university of Tuebingen
03/1995-02/1996	Diploma thesis at the department of organic chemistry (Prof. Dr. Guenther Jung) at the university of Tuebingen Title: "Heterologe Expression eines antifungischen Proteins in *E. coli*"
05/1996-11/1999	Dissertation at the department of organic chemistry (Prof. Dr. Guenther Jung) at the university of Tuebingen Title: "RNA-Vakzine" Certificate: diploma
11/1999-10/2001	Executive education at the university "Donauuniversität Krems" in Austria Certificate: MBA

Professional Experience:

12/1999-09/2000	Scientist at the department of organic chemistry (Prof. Dr. Guenther Jung) at the university of Tuebingen
10/2000-01/2002	freelancing consultant for the organization "Verband BioRegio Stuttgart"
2000	Foundation of CureVac GmbH in Tuebingen, Germany
since 02/2002	CEO of CureVac GmbH in Tuebingen, Germany

Publication list:

Scheel B, Aulwurm S, Probst J, Stitz L, Hoerr I, Rammensee HG, Weller M, Pascolo S. Therapeutic anti-tumor immunity triggered by injections of immunostimulating single-stranded RNA. Eur J Immunol 2006; 2:2807-2816

Probst J, Brechtel S, Scheel B, Hoerr I, Jung G, Rammensee HG, Pascolo S. Characterization of the ribonuclease activity on the skin surface. Genet Vaccines Ther 2006; 4:4.

Carralot JP, Weide B, Schoor O, Probst J, Scheel B, Teufel R, Hoerr I, Garbe C, Rammensee HG, Pascolo S. Production and characterization of amplified tumor-derived cRNA libraries to be used as vaccines against metastatic melanomas. Genet Vaccines Ther 2005; 3:6.

Teufel R, Carralot JP, Scheel B, Probst J, Walter S, Jung G, Hoerr I, Rammensee HG, Pascolo S. Human peripheral blood mononuclear cells transfected with messenger RNA stimulate antigen-specific cytotoxic T-lymphocytes in vitro. Cell Mol Life Sci 2005; 62:1755-62.

Scheel B, Teufel R, Probst J, Carralot JP, Geginat J, Radsak M, Jarrossay D, Wagner H, Jung G, Rammensee HG, Hoerr I, Pascolo S. Toll-like receptor-dependent activation of several human blood cell types by protamine-condensed mRNA. Eur J Immunol 2005; 35:1557-66.

Carralot JP, Probst J, Hoerr I, Scheel B, Teufel R, Jung G, Rammensee HG, Pascolo S. Polarization of immunity induced by direct injection of naked sequence-stabilized mRNA vaccines. Cell Mol Life Sci 2004; 61:2418-24.

Hoerr I, Obst R, Rammensee HG, Jung G. In vivo application of RNA leads to induction of specific cytotoxic T lymphocytes and antibodies. Eur J Immunol 2000; 30:1-7.

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Exhibit B

RNActive

Summary of experiments

1. In vitro transcription:

The recombinant plasmid DNA was linearized and subsequently in vitro transcribed using the T7 RNA polymerase. The DNA template was then degraded by DNAseI digestion. The RNA was recovered by LiCl precipitation and further cleaned by HPLC extraction (Pure Messenger™, CureVac GmbH, Tübingen, Germany).

2. Complexation with protamine

For complexation the RNA was mixed with protamine at a ratio of 8:1.

Mouse Model

3. Preventive vaccination of mice with wild type or GC-enriched mRNA coding for the antigen Ovalbumin

3.1. Methods:

Animals: C57BL/6

Tumor cells: E.G7-OVA (syngenic lymphoma cells which stably express the antigen Ovalbumin) (ATTC, Manassas, VA)

Reference: Cell. 1988 Sep 9;54(6):777-85.

Model Antigen: Ovalbumin

Groups: 5 mice per group

- **OVA wt**: wild type mRNA coding for Ovalbumin, complexed with protamine
- **OVA GC**: GC-enriched mRNA coding for Ovalbumin, complexed with protamine
- **Protamine**: protamine without RNA
- **Control**: untreated

Immunization: 20 µg mRNA (10 µg per ear) complexed with protamine were injected intradermally into the mice followed one day later with s.c. injection

(subcutaneously) of GM-CSF. The immunization was repeated 7 times within 3 weeks. Blood samples were taken from the mice one day before the tumor cells were injected in the mice and the presence of antibodies against Ovalbumin was measured by ELISA (3.1.1. B-cell immune response).
One week after the last immunization, 1 Mio E.G7-OVA tumor cells were subcutaneously injected in the mice. After 12 days, tumor volume was determined.

3.1.1. Detection of an antigen-specific immune response (B-cell immune response):

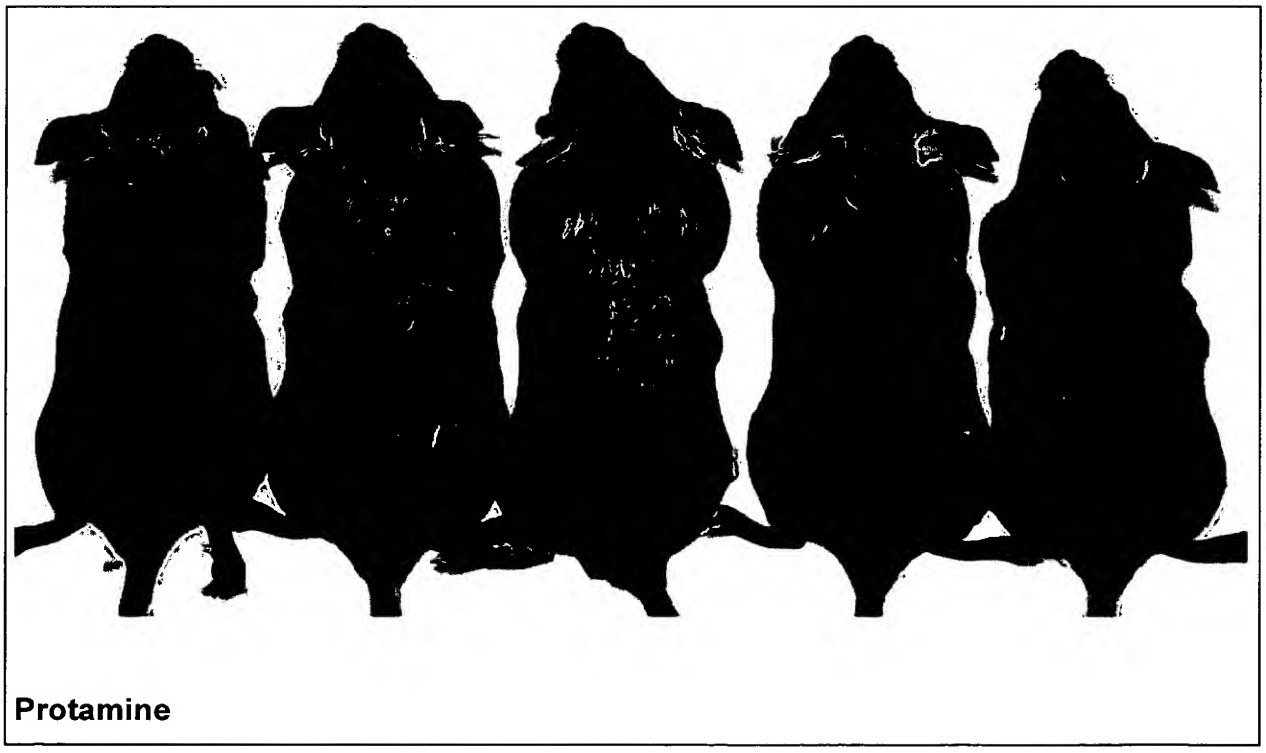
For detection of antigen-specific antibodies, blood samples were taken from the vaccinated mice and sera were prepared. MaxiSorb plates (Nalgene Nunc International) were incubated with the antigen (Ovalbumin). After blocking with 1×PBS containing 0,05% Tween-20 and 1% BSA the plate was incubated with diluted mouse serum (1:80, 1:40, 1:20, 1:10 and 1:5). Subsequently a biotin-coupled secondary antibody (Anti-mouse-IgG1 von Caltag, Burlington, USA) was added. After washing, the plate was incubated with Horseradish peroxidase-streptavidin and subsequently the conversion of the ABTS substrate (2,2'-azino-bis(3-ethyl-benzthiazoline-6-sulfonic acid) was measured.
⇒ the conversion of the ABTS substrate indicates the presence of antigen-specific antibodies

3.2. Results:

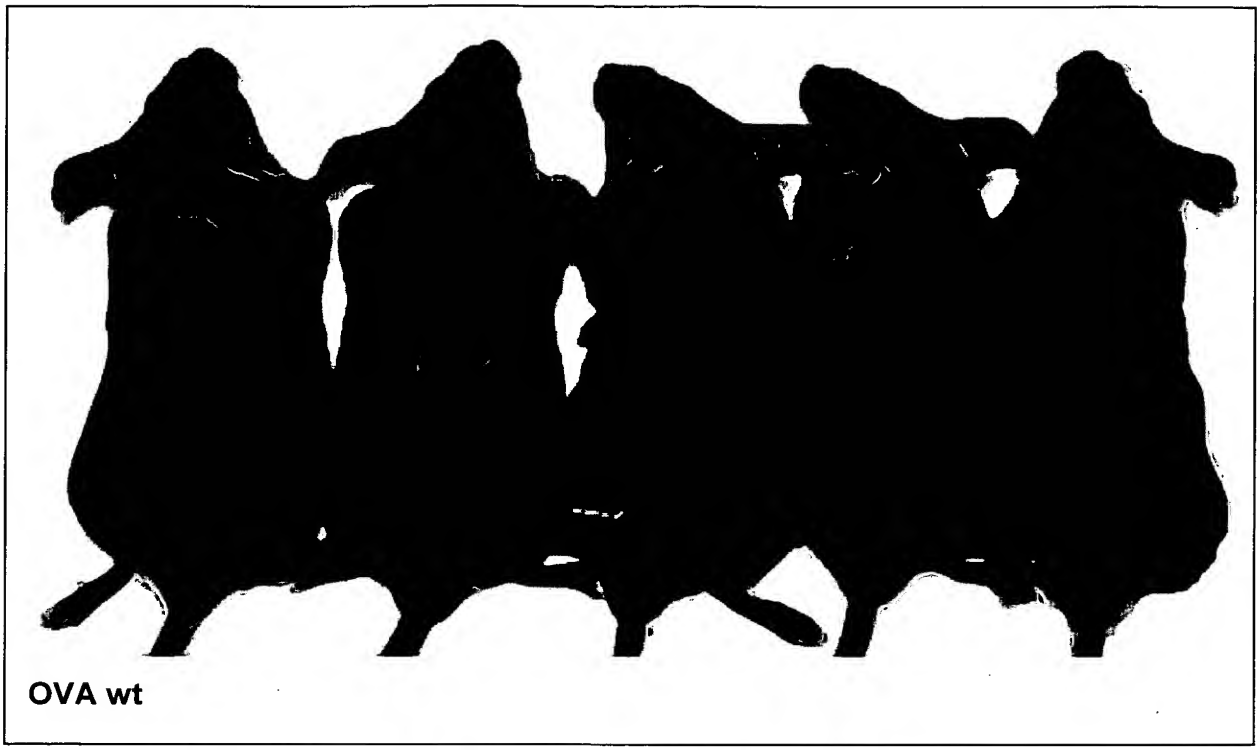
3.2.1. Determination of tumor growth following vaccination with wild type or GC-enriched mRNA coding for Ovalbumin:

Images of the mice:

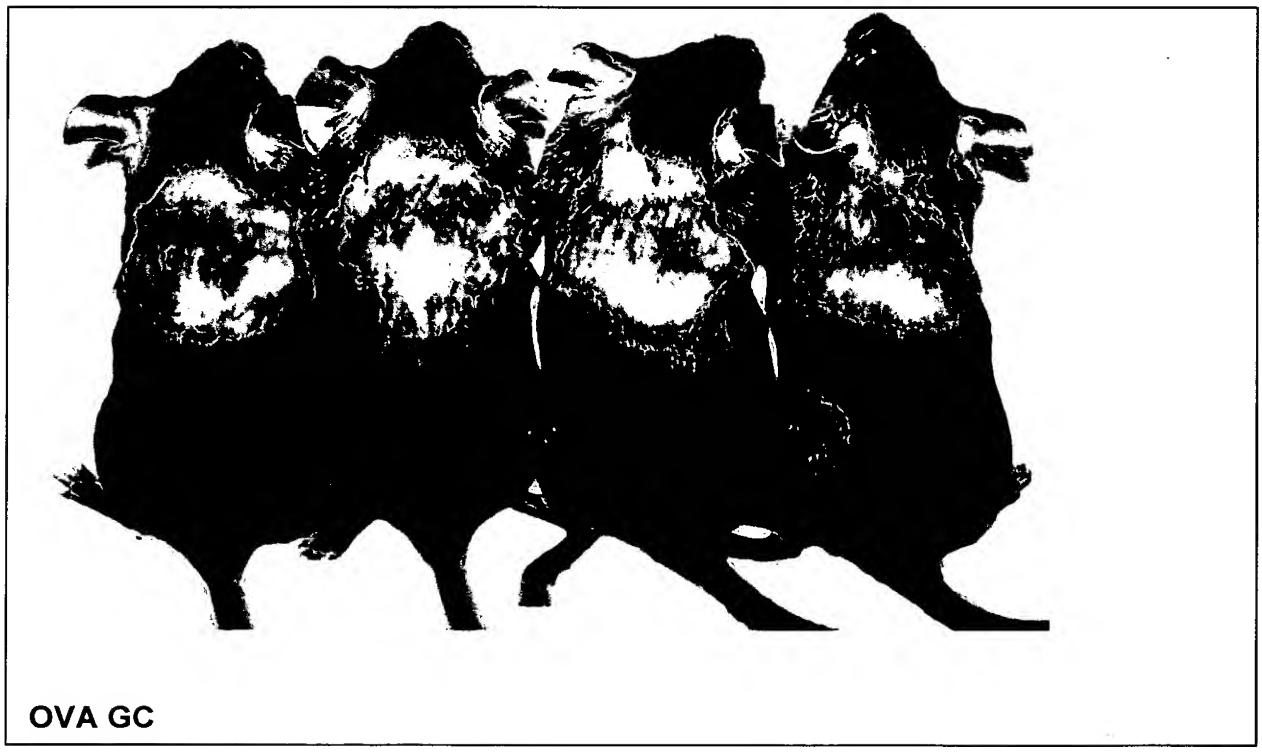
Control



Protamine

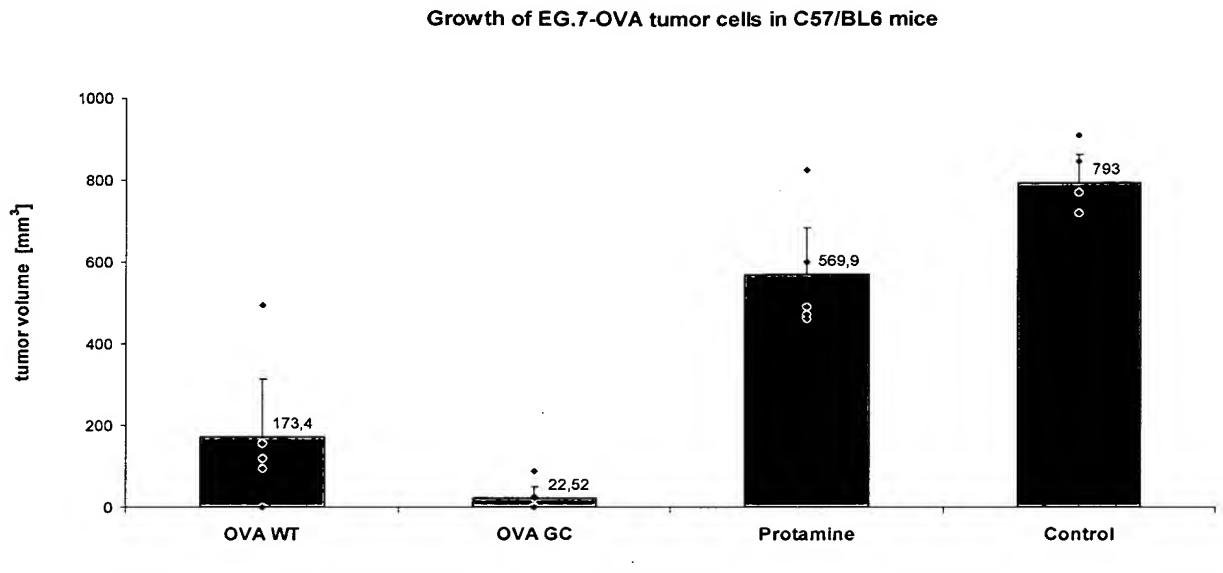


OVA wt



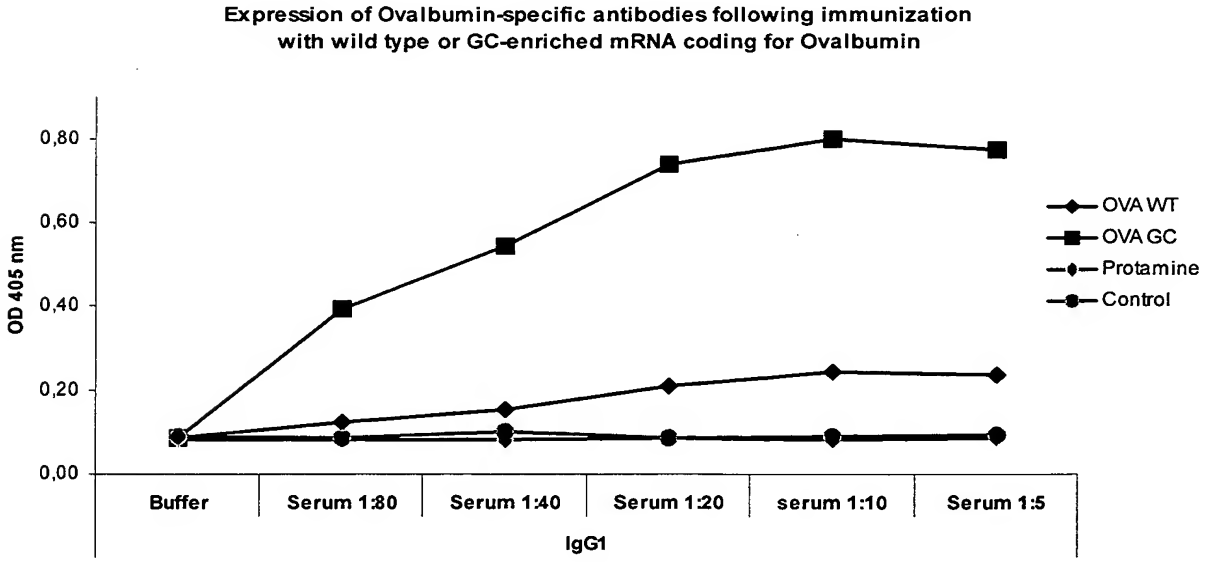
OVA GC

Determination of the tumor volume:



This experiment clearly shows that the preventive immunization with GC-enriched mRNA coding for Ovalbumin inhibits the growth of syngenic tumor cells expressing the antigen Ovalbumin. The wild type mRNA coding for Ovalbumin also reduces the tumor growth but it is not able to the same degree as immunization with GC-enriched mRNA.

3.2.2. Detection of an antigen-specific immune response (B-cell immune response)



The determination of antibodies against Ovalbumin in the sera show that the mice vaccinated with GC-enriched mRNA produce much more IgG1 antibodies against Ovalbumin than the mice vaccinated with wild type mRNA.

4. Expression of Luciferase *in vivo* after intradermal injection of wild type or GC-enriched mRNA

4.1. Methods:

Animals: Balb/c

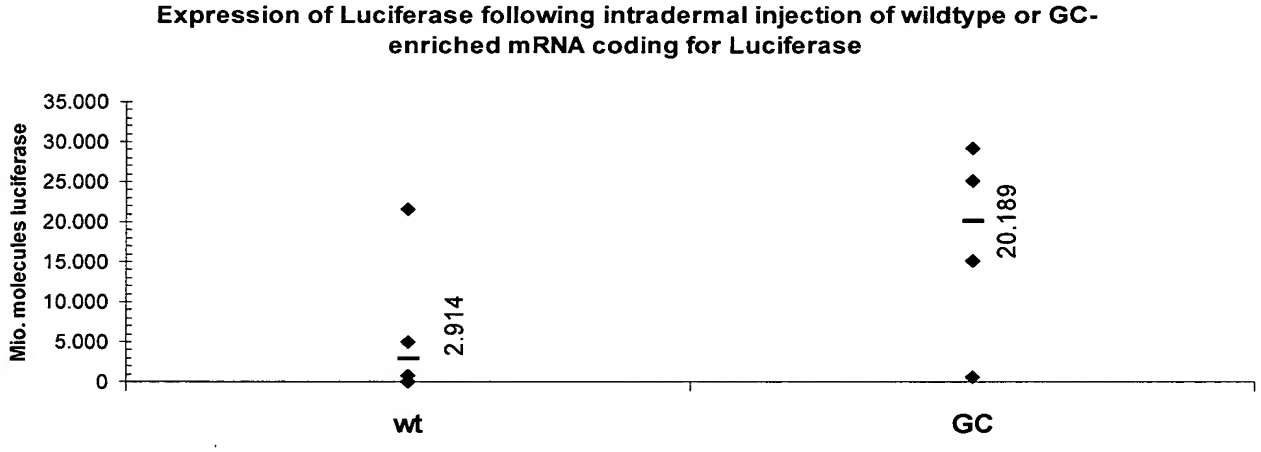
Antigen: Luciferase

Groups: 4 mice per group

Injection of mRNA: Wild type or GC-enriched mRNA coding for Luciferase (stabilized with protamine) were injected intradermal into mice.

Determination of Luciferase expression: After 24h, Luciferin (Synchem) was injected intraperitoneal and the luminescence was measured with a CCD camera (Orca II, Hamamatsu). The data were analysed with the SimplePCI Software (Hamamatsu).

4.2. Results:



This experiment shows that GC-enriched mRNA coding for Luciferase results in higher expression levels of Luciferase *in vivo* than wild type mRNA following interdermal injection in mice.

5. Induction of a CTL immune response by vaccination of mice with wild type or GC-enriched mRNA coding for the Influenza A matrix protein M1 (Flu)

The mice were injected (intradermally) several times with wild type or GC-enriched mRNA coding for the Influenza A matrix protein M1 (Flu) (complexed with protamine). Additionally, the mice were stimulated with GM-CSF (subcutaneously).

5.1. Methods:

Detection of an antigen-specific immune response (CTL immune response):

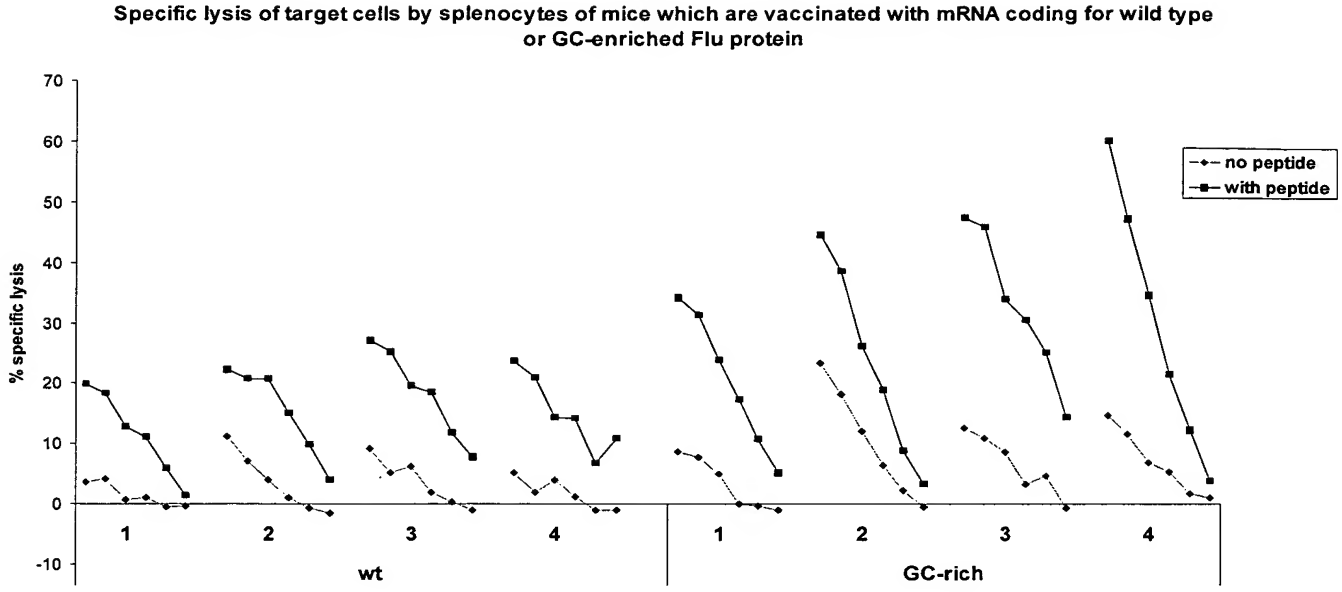
- Removal of the spleen
- Extraction of splenocytes

Detection of apoptosis of target cells:

Cr-Release:

Splenocytes (effector cells) were stimulated in vitro for 6 days with Flu peptide and the CTL activity of RMA-S HHD cells were determined using a [^{51}Cr] release assay. Therefore the RMA-S HHD cells were labelled for 2h with [^{51}Cr] and subsequently incubated for 5h with the stimulated effector cells. Chromium release was measured using a solid-phase scintillation plate (Luma Plate-96, Packard) and a microplate format scintillation counter (1450 Microbeta Plus, Wallac, Perkin Elmer).

5.2. Results:



Analysis of the CTL response of mice following vaccination with wild type or GC-enriched mRNA coding for the Influenza A matrix protein M1 (Flu) showed that GC-enriched mRNA induces a higher CTL response specific against Flu compared to the wild type mRNA.

Human model:

6. Expression of Luciferase in hPBMCs following transfection with wild type or GC-enriched mRNA

6.1. Methods:

Model Antigen: Luciferase

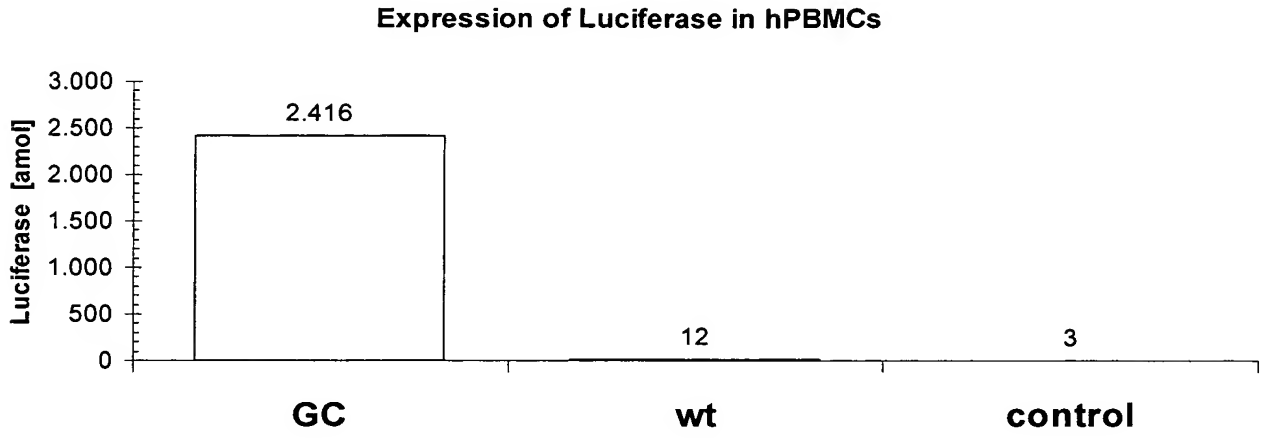
Cells: hPBMCs

Transfection: Human PBMCs were electroporated with the EasyjecT Plus (Peqlab, Erlangen, Germany) with wild type or GC-enriched mRNA coding for Luciferase. The control cells were not transfected.

Detection of Luciferase: 16h after electroporation the cells were lysed with Lysis Buffer (25 mM Tris-PO_4, 2 mM EDTA, 10% Glycerol, 1% Triton-X 100, 2 mM DTT). Supernatants were mixed with Luciferin Buffer (25 mM Glycylglycin, 15 mM $MgSO_4$,

5 mM ATP, 62,5 µM Luciferin) and the luminescence was measured with a luminometer (Lumat LB 9507; Berthold Technologies, Bad Wildbad, Germany).

6.2. Results:



The results show that transfection of hPBMCs with GC-enriched mRNA coding for Luciferase leads to a higher expression of Luciferase compared to the wild type mRNA.

7. Determination of the immunostimulatory effect of different mRNAs by measuring the release of the cytokines IL-6 and TNFα:

7.1. Methods:

Model Antigen: Influenza A matrix protein M1 (Flu)

Cells: hPBMCs

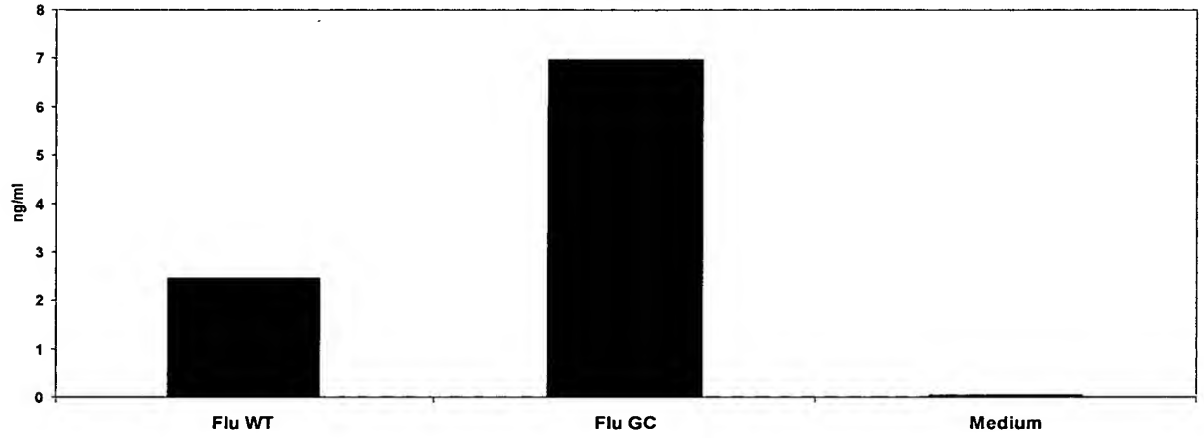
Human PBMCs were isolated from blood samples of different donors. hPBMCs were prepared by Ficoll density gradient centrifugation (PAA Laboratories, Austria). The hPBMCs were incubated with wild type or GC-enriched mRNA coding for an antigen (stabilized with protamine) and after 16h supernatant samples were taken. ELISA plates (Nunc Maxisorb) were coated overnight with capture antibodies (BD Pharmingen, Heidelberg, Germany) and afterwards blocked with 1×PBS containing 1% BSA (bovine serum albumin). The supernatants were added and incubated for 4h. Subsequently a biotin-coupled secondary antibody was added. After washing the plate was incubated with Horseradish peroxidase-streptavidin and subsequently the conversion of the ABTS substrate (2,2'-azino-bis(3-ethyl-benzthiazoline-6-sulfonic

acid) was measured. The quantification of the cytokines IL-6 (Interleukin-6) and TNFα (Tumor necrosis factor alpha) was carried out via a standard curve with recombinant proteins (BD Pharmingen, Heidelberg, Germany).

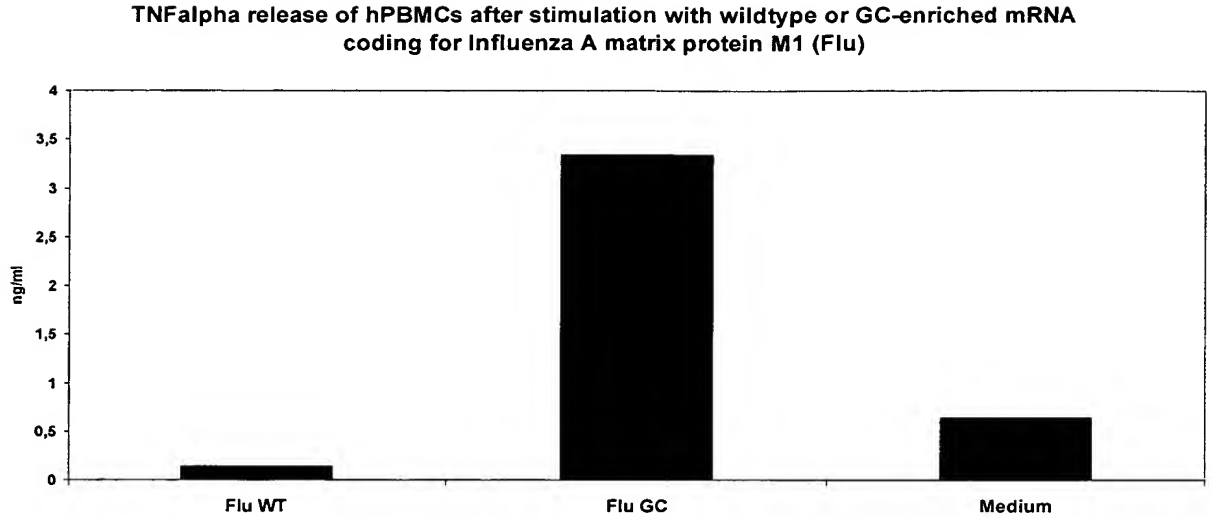
⇒ The release of cytokines like IL-6 and TNFα indicates the immunstimulatory effect of a mRNA

7.2. Results:

IL-6 release of hPBMCs after stimulation with wildtype or GC-enriched mRNA coding for Influenza A matrix protein M1 (Flu)



IL-6 release indicates the induction of a humoral immune response, which leads to production of antigen-specific antibodies which recognize the antigen on the surface of antigen-presenting cells and thereby induce the lysis of the cells.



TNFα release indicates the activation of macrophages and therefore a cell-mediated immune response, which can kill antigen-presenting cells.

We could show that GC-enriched mRNA coding for the Influenza A matrix protein M1, as a model antigen, has better immunostimulatory properties than the wild type mRNA.

8. **Vaccination of a tumor patient with mRNA coding for CEA, Mucin-1, Her2/neu, Survivin, MAGE-1, HBS and Flu**

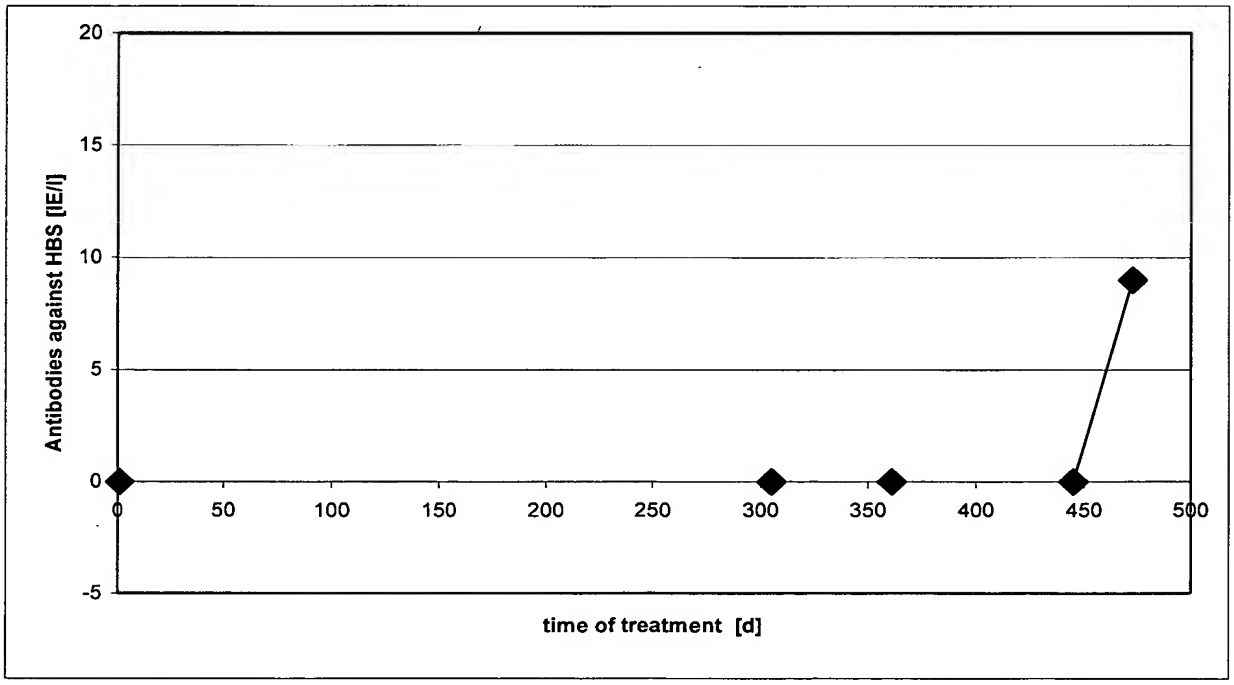
Phase I/II study for evaluation of efficiency of mRNA-vaccination in patients with malignancies.

Method: The patient was injected 4 times with 150 µg mRNA coding for HBS (GC-enriched) CEA, Mucin-1, Her-2/neu, Survivin, MAGE-1, and Influenza A Matrix protein M1 (Flu). The titer of antibodies against HBV were analyzed using a standard method in the clinic.

8.1. Tumor rejection:

Results: A regression of the tumor is visible in the computer tomography (CT). This clinical trial proves that vaccination of tumor patients with mRNA coding for tumor antigens and viral antigens induces the immune system to reject the tumor cells.

8.2. Induction of HBS-specific antibodies



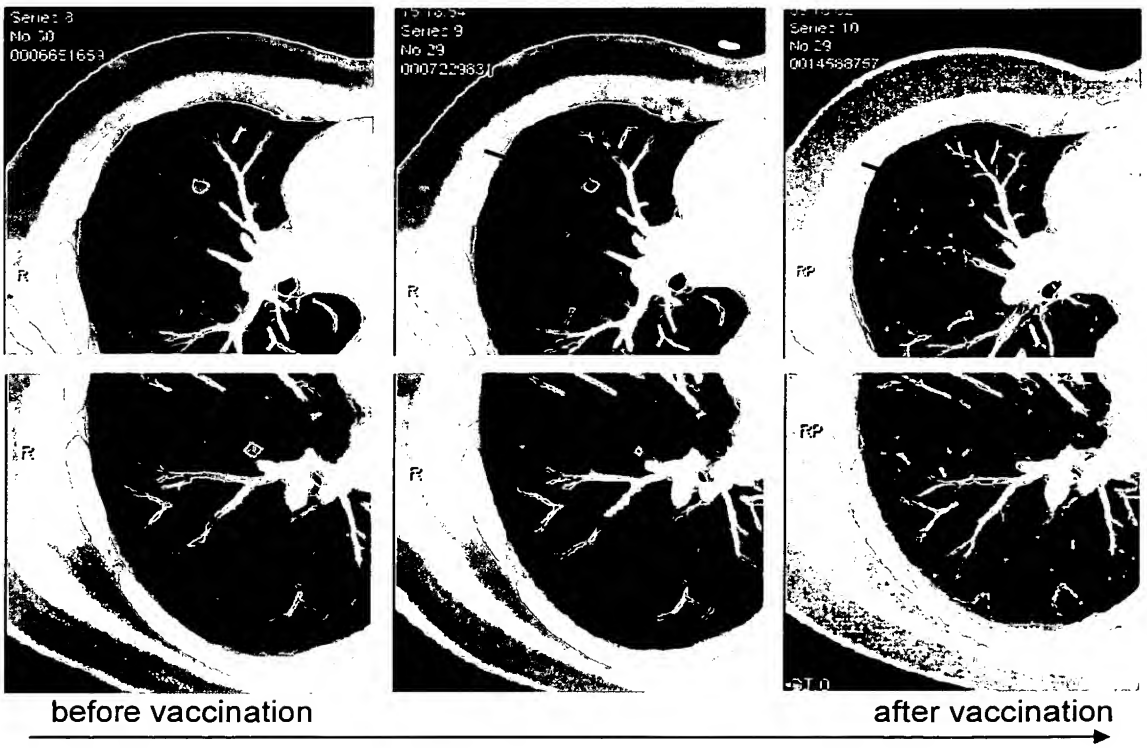
Results: This trial shows that vaccination with mRNA coding for tumor antigens and viral antigens can induce antigen-specific antibodies against the viral hepatitis B surface (HBS) antigen.

Viral antigens were used in this trial to increase the immune response against the tumor antigens, because viral antigens are very immunogenic and most people had an infection with influenza, thus the immune system becomes stimulated very strongly. They were additionally used as markers for induction of an immune response because the detection of HBS antibodies is a standard procedure in the clinic.

9. **Tumor regression after intradermal injection of mRNA coding for Melan-A, Tyrosinase, Survivin, MAGE-A3, MAGE-A1, gp100, HBS and Flu**

Phase I/II study for evaluation of efficiency of mRNA-vaccination in patients with malignancies.

Method: The patient was injected 11 times with 80 µg mRNA/antigen coding for HBS (GC-enriched), Melan-A, Tyrosinase, Survivin, MAGE-A3, MAGE-A1, gp100, and Influenza A Matrix protein M1 (Flu) complexed with protamine (5:1).



Results: A regression of the tumor is visible in the computer tomography (CT). This clinical trial proves that vaccination of tumor patients with mRNA coding for tumor antigens induces the immune system to reject the tumor cells.